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Direct Comparison of Apremilast and Best Supportive Care Using a Discrete Event Simulation

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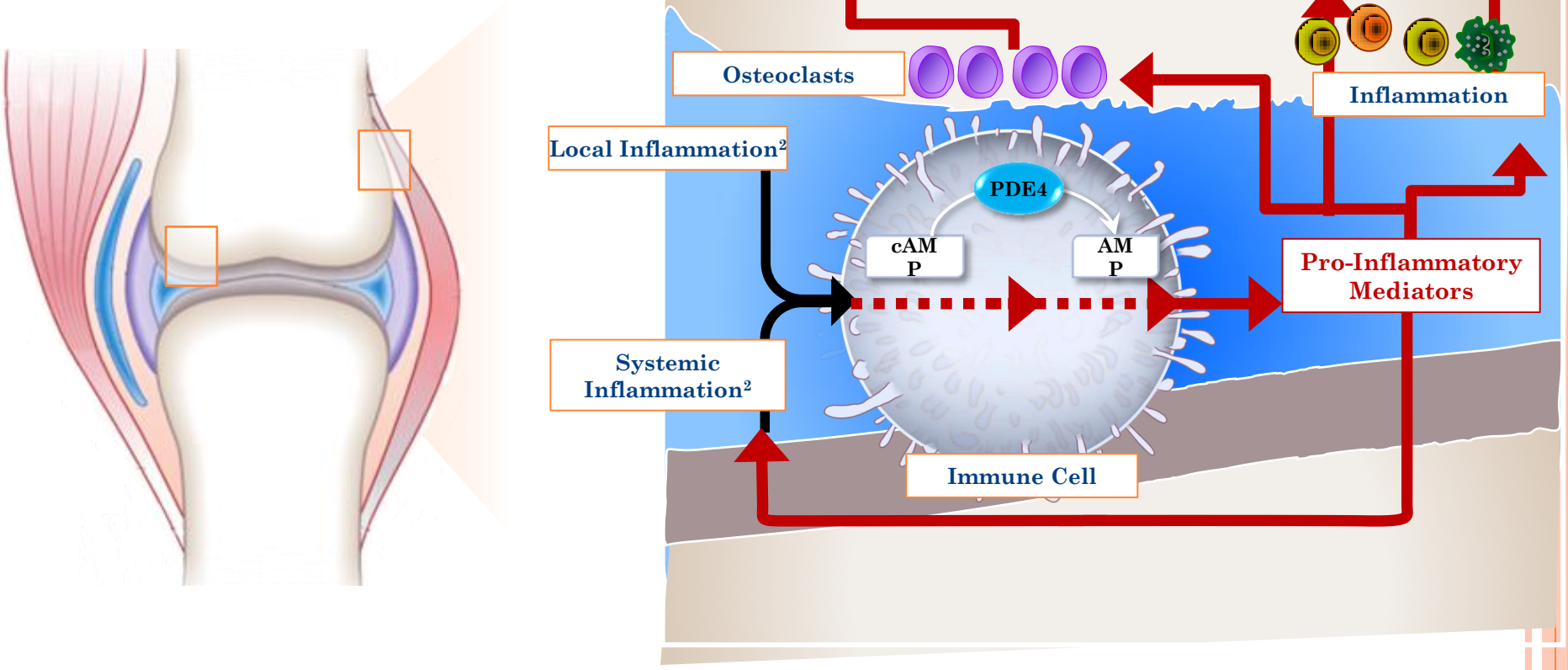
Outline

- Psoriatic Arthritis Disease Brief
  - Mechanism of action
  - Differences between Psoriatic Arthritis and Rheumatoid Arthritis
  - Current treatment
- Discrete Event Simulation
  - Definition
  - Model Overview
  - Model Results

Psoriatic Arthritis Disease Brief

PsA Is a Chronic Inflammatory Disease of the Joints and Skin Resulting From an Uncontrolled Immune Response[1]



Over-production of TNF-α as well as other cytokines, alters bone homeostasis, resulting in the joint damage seen in PsA[4]

1. Schafer. *Biochem Pharmacol*. 2012;83:1583
2. Serezani et al. *Am J Respir Cell Mol Biol*. 2008;39:127
3. Gottlieb et al. *J Am Acad Dermatol*. 2008;58:851
4. Mensah et al. *Curr Rheumatol Rep*. 2008;10(4):311

PsA differs from Rheumatoid Arthritis (RA) based on the presence of psoriatic-associated conditions and the distribution and appearance of the affected joints

Clinical Feature	PsA	RA
Psoriatic skin lesions present	Common	No
Psoriasis-associated nail symptoms	Common	No
Distribution of affected joints	Often asymmetrical Various joints affected	Symmetrical Primarily involving hands and wrists
Appearance of the affected joint	More generalized swelling Produce a sausage-like appearance in fingers or toes	Pronounced swelling over joints (RA nodules)
Disease progression	Variable	Predictable
Rheumatoid factor status	Seronegative	Seropositive

3. Gottlieb A, et al. *J Am Acad Dermatol.* 2008 May;58(5):851-64.

Key concepts

- In 75% of cases, psoriasis precedes the joint disease.
- In 15% of cases, the onset of skin disease is at the same time as onset of joint involvement.
- In 10% of cases, the joint disease precedes the psoriasis.

PsA and QoL

- For people with psoriatic arthritis, quality of life is impacted by both the physical symptoms of the disease and the emotional burden of sometimes disfiguring skin symptoms.
- Compared to rheumatoid arthritis and ankylosing spondylitis, people with psoriatic arthritis report more psychosocial problems.
- This finding fits with data from a survey of people with psoriasis, which found that 75 percent of patients believe the skin condition had a moderate to large negative impact on their quality of life, with alteration in their activities and work.

5. Husted JA, et al. Arthritis Rheum. Apr 2001;45(2):151-158.
6. Salaffi F, et al. Health Qual Life Outcomes. 2009;7:25.
7. Bhosle MJ, et al. Health Qual Life Outcomes. 2006;4:35.

PsA has a significant negative impact on health-related quality of life (HRQoL)

- Decreased QoL as measured by the Medical Outcomes Short-Form 36 Questionnaire (SF-36) scores in patients with PsA compared to the general population:[1]
- 19% of patients with PsA claimed their disease resulted in "marked physical limitations"[2]
- 8.2% of patients sought assistance for home activities from friends or family[3]
- Both physical functioning and emotional well-being are decreased.
- In patients with PsA and psoriasis:
  - Arthritis component - greater impact on physical functioning
  - Psoriasis component - greater impact on emotional well-being
    - Skin lesions associated with poor self-image and distress from pruritus and pain.

[8]Husted JA, et al. *J Rheumatol*. 1997 Mar;24(3):511-7.
[9]Torre Alonso JC, et al. *Br J Rheumatol*. 1991 Aug;30(4):245-50.
[10]Kimball AB, et al. *J Drugs Dermatol*. 2007 Mar;6(3):299-306.

Epidemiology

Prevalence	5% - 40% of people with psoriasis
Race	Affects Caucasians more than other races
Gender	Men and women equally affected
Age of onset	40–50 years of age, can occur earlier

11. Gladman DD. *Rheum Dis Clin North Am* 1992;18:247–56

Treatment Options

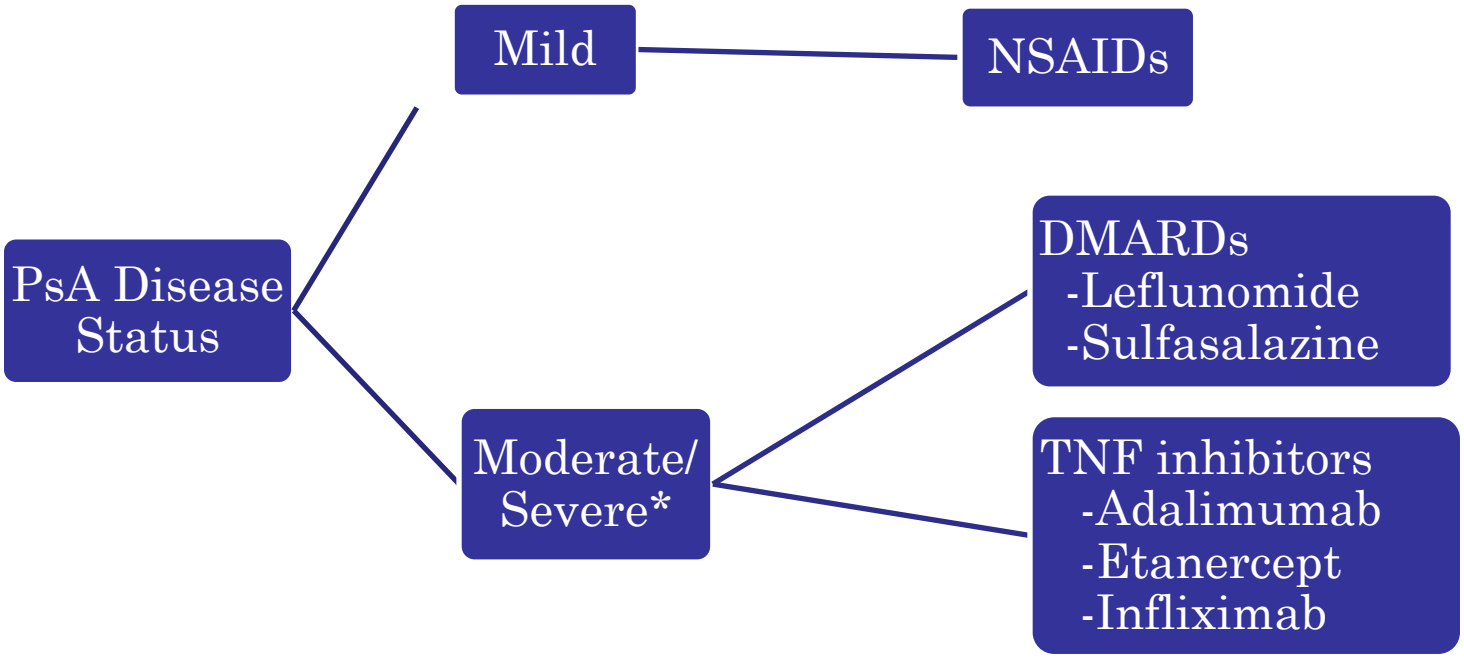
Mild Disease

- NSAIDs

Moderate to Severe Disease

- Corticosteroids
- Traditional DMARDs
  - MTX
  - Sulfasalazine
  - Leflunomide
- Biologic DMARDs

National Guideline Recommendations in Patients with PsA



*No evidence supporting DMARDs ahead of TNF inhibitors (effect size: TNF inhibitors > traditional DMARDs). However, TNF inhibitors are recommended for patients who fail to respond to at least one DMARD therapy unless poor prognosis present.

Grade A=Based on evidence from meta-analysis of randomized controlled trials (RCT) or ≥ 1 RCT

12. Ritchlin CT, et al. *Ann Rheum Dis*. 2009 Sept;68(9): 1387-94.

Adverse Effects Limit the Benefits of Therapy with Traditional Systemic DMARDs and Biologics

- **Traditional systemic agents**
  - Methotrexate (MTX) has weak and conflicting evidence in the management of PsA with risks of serious toxic reactions.
  - MTX is not approved by the FDA
  - Leflunomide does not have FDA approval and requires monitoring for hepatic toxicity
  - Sulfasalazine has limited evidence in the management of PsA with rarely occurring serious toxicities.
- **Biologics**
  - Mild injection-site/infusion reactions
  - Black box warning of risk of serious infections and malignancies
    - Increased risk of infection
      - Overall infections, odds ratio 1.18 (95% confidence interval, 1.05-1.33)[2]
    - Patients with PsA are at greater risk for mortality from infection.

13. Enbrel Prescribing Information, http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf

The Significant Burden Associated with PsA

- **Patients with PsA:**
  - Suffer from limited mobility, pain, inflammation and stiffness as well as skin lesions from psoriasis
  - Have a poorer quality of life
  - Are less likely to be employed and less likely to be productive
  - Incur higher healthcare costs

- **New PsA therapies are needed that demonstrate:**
  - Effective Treatment in Patients with Active Psoriatic Arthritis
  - Improved Safety and Better Tolerability than Traditional DMARDS and Biologics
  - Patient Convenience over Injectable Biologics
  - Cost savings compared to Biologics

Apremilast

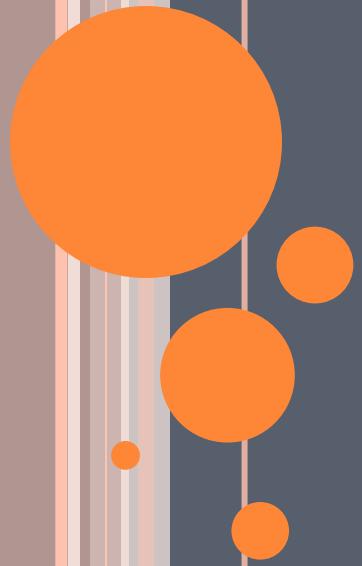
- Apremilast is a first-in-class PDE4 inhibitor
  - MOA: modulates pro-inflammatory and anti-inflammatory mediators
  - Administration: oral and does not need dose adjustments

- This drug represents a novel treatment option for patients and can represent a delay in biologic therapy[14]

14. Tencer T, et al. (2014) Economic evaluation of sequencing strategies in the treatment of psoriatic arthritis in the United States (abstract). Value in Health (17)3: A46.

Outcome measures of PsA

- ACR response criteria: 20%, 50%, 70%
  (validated in RA, not PsA)
  - Tender and swollen joint count
    (modified for PsA to include DIP and CMC joints: 78/76, 68/66)
  - 3/5: patient global, physician global, patient pain, HAQ, acute phase reactant (sed rate, CRP)
- Psoriatic Arthritis Response Criteria (PsARC)
  - Improvement in at least 2 of 4 criteria, including:
    - Physician global assessment (0–5)
    - Patient global assessment (0–5)
    - Tender joint score (≥ 30%)
    - Swollen joint score (≥ 30%)
  - Improvement in at least 1 of 2 joint scores
  - No worsening in any criteria



Discrete Event Simulation

All Models Are Wrong, But Some Are Useful

-George E.P. Box

Discrete Event Simulation (DES)

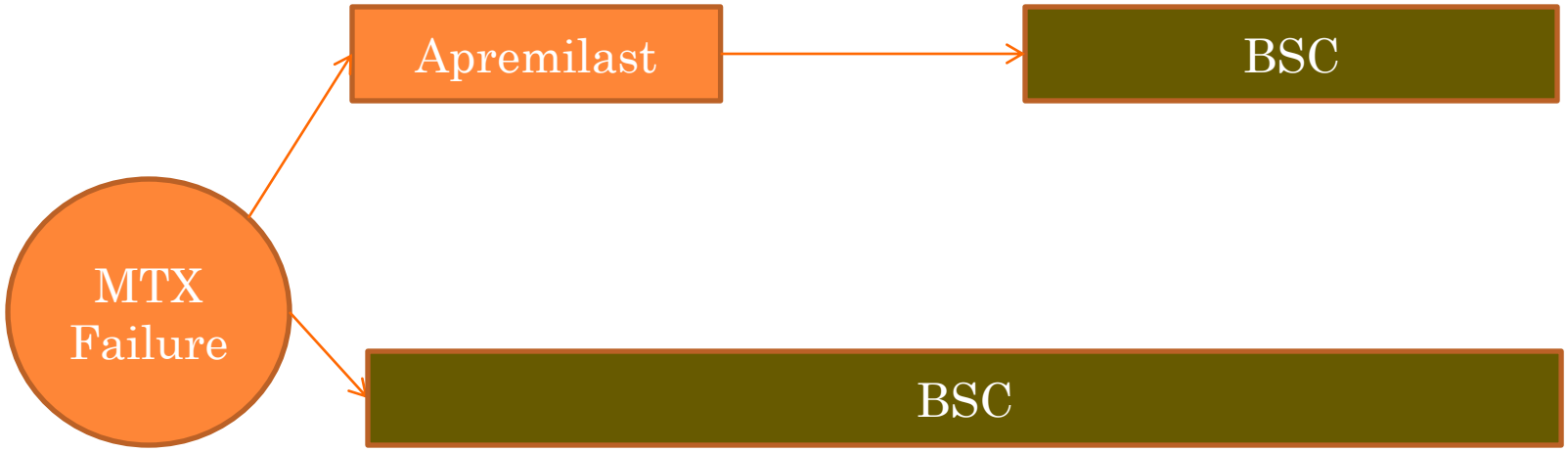
- DES is a modeling technique that is event-based

Advantages vs Markov Models

- DES can incorporate new data as it becomes available
- Can use an individual patient's values and examine the decision from his or her point of view
- Can capture multiple events with competing risks

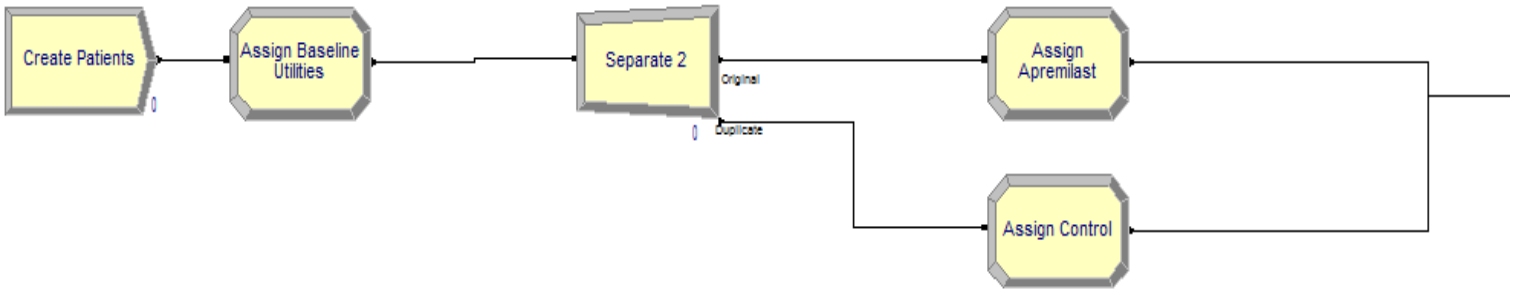
Basic Model Structure

- Patients with active psoriatic arthritis who have failed methotrexate (MTX) therapy will be split into two groups: apremilast followed by best supportive care (BSC) and patients only receiving BSC



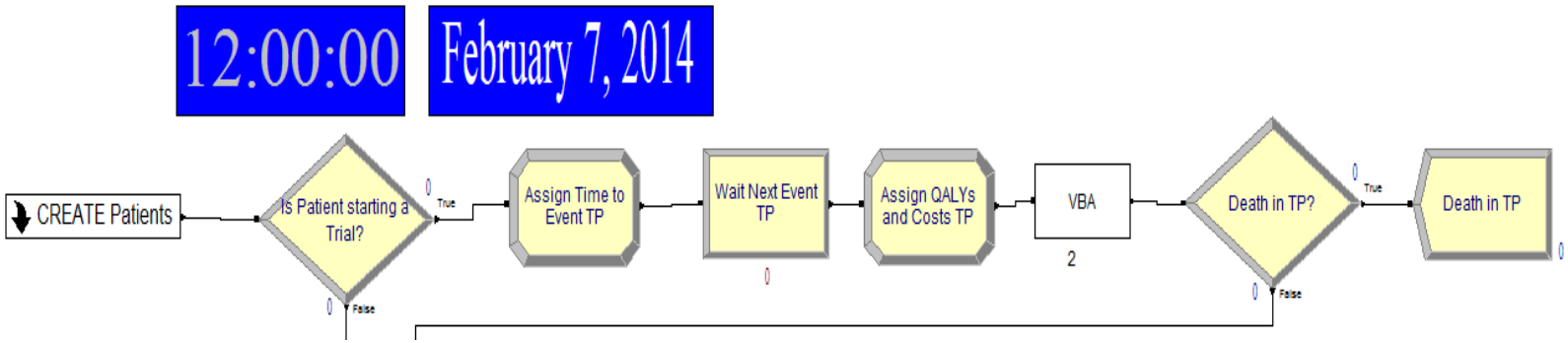
Step 1: Create patients and assign characteristics

- Assign Baseline Utilities:
  - Age
  - Gender (45% male)
  - Life expectancy
  - Mortality



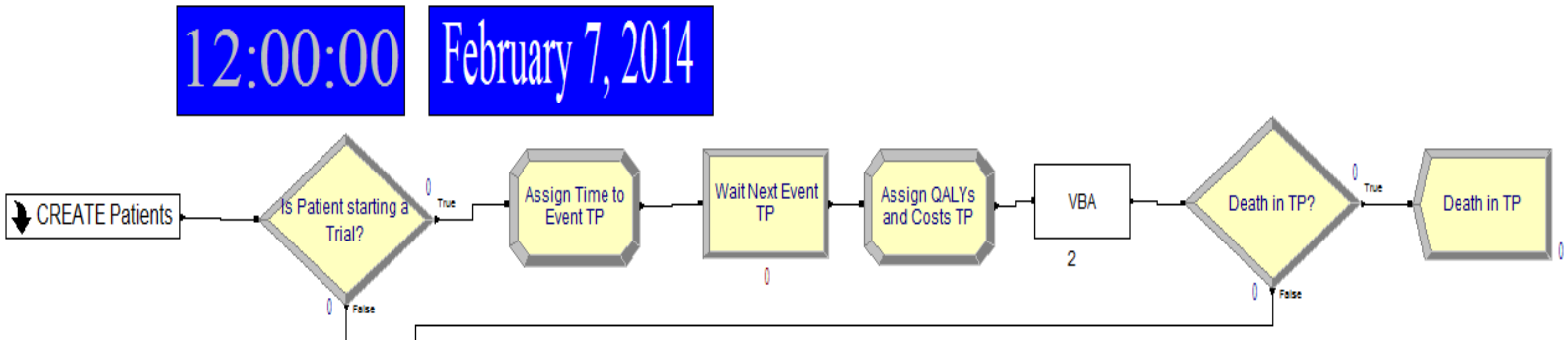
Step 2: Patients enter either APR or BSC treatment arm

- If 'Is Patient starting a Trial?' is TRUE, then patients enter APR arm
- 'Assign Time to Event TP' sets the next event to death and logs the time at the beginning of the time-to-event period
- Time advances in "Wait Next Event TP"



Step 2: Patients enter either APR or BSC treatment arm

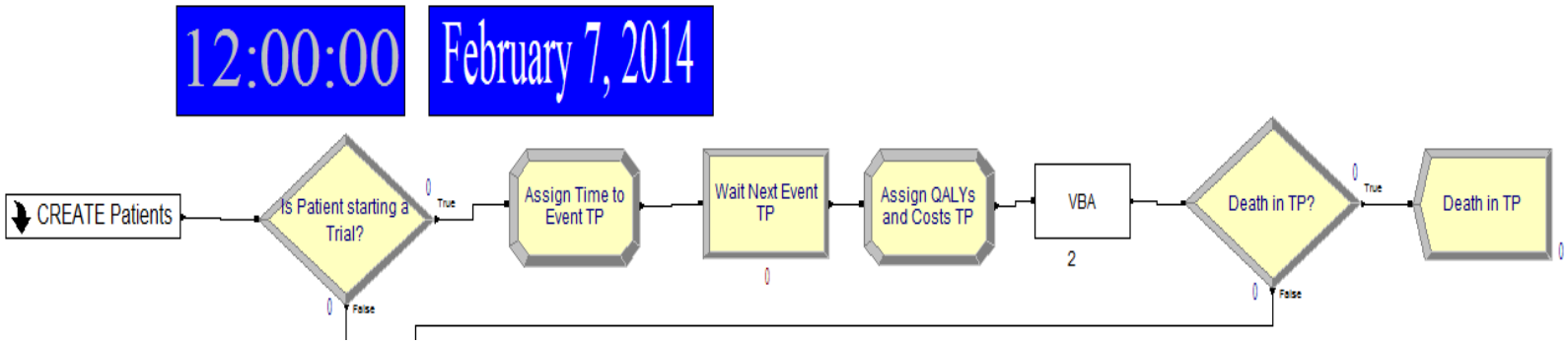
- Patients move to 'Assign QALYs and Costs TP' where QALYs and Costs are calculated
- The VBA module is used to calculate Other Healthcare Costs
  - The VBA module computes the patient's age each month and tallies the costs over the course of the period



Step 2: Patients enter either APR or BSC treatment arm

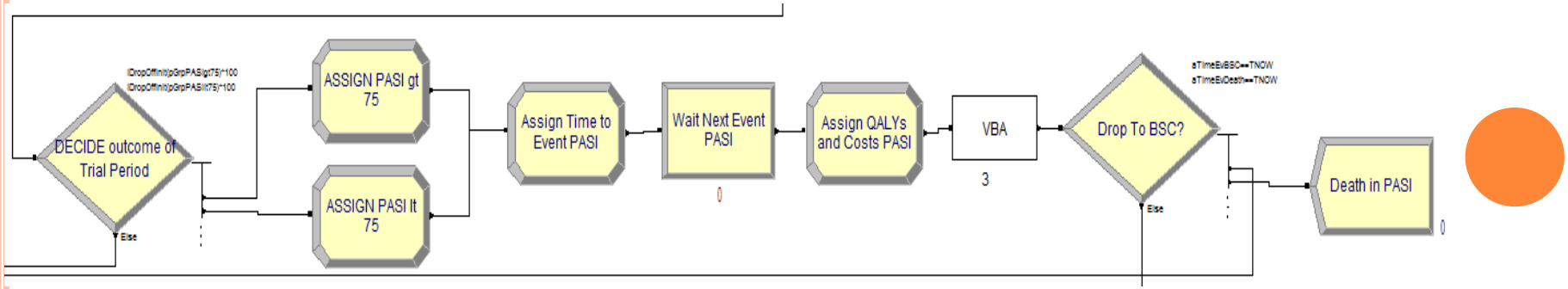
- After costs and QALYs have been assigned, 'Death in TP?' checks to see if the time of death event was prior to the end of the Trial Period

- If so, patient is disposed of in the model, otherwise patient continues to BSC



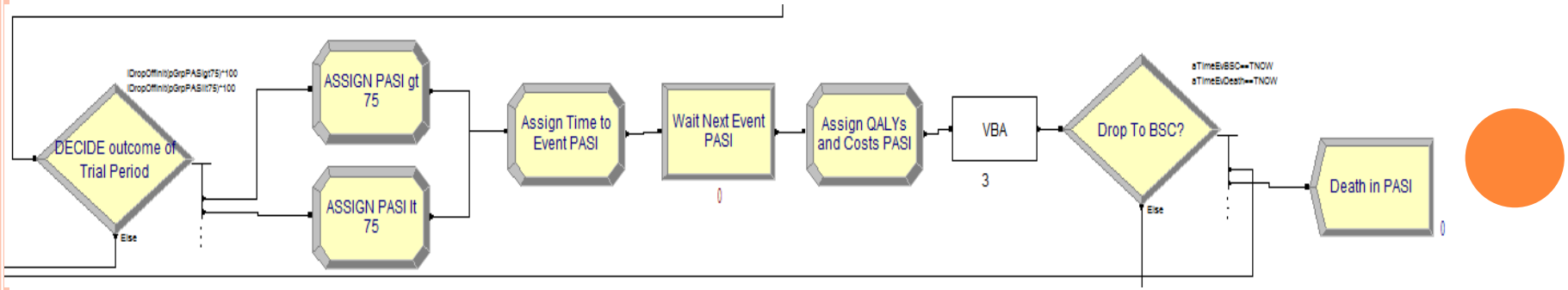
Step 3: Decide if treatment was effective (or not)

- Patients enter a decision module ('DECIDE outcome of Trial Period') which decides whether the patients achieved a PsARC score (effective treatment) or not
- If treatment effective, patients are assigned to a PASI group to allocate future costs and QALYs
- Patients who are not successfully treated move to the BSC arm



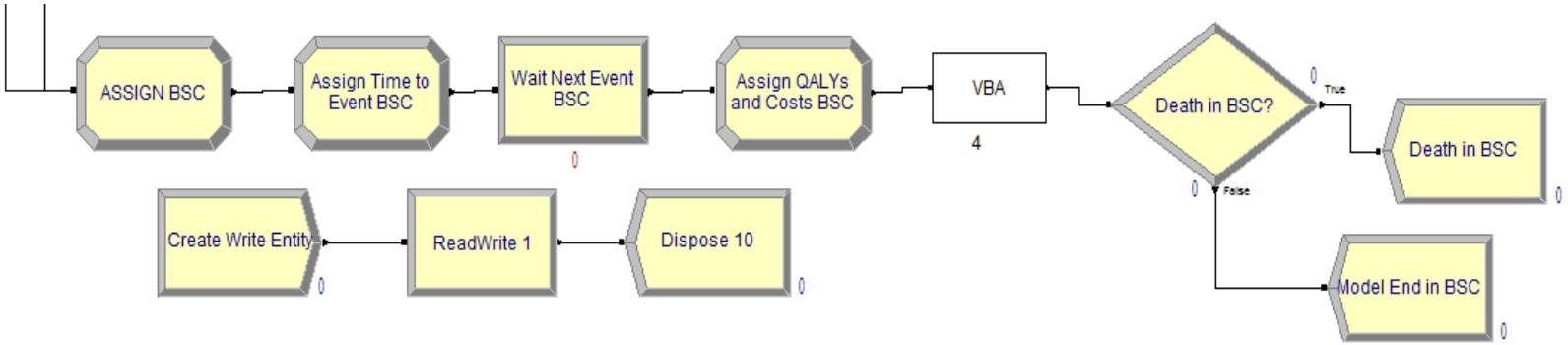
Step 3: Decide if treatment was effective (or not)

- 'Assign Time to Event PASI' module assigns a length of time until patients move to BSC
- Similar to the Trial Period arm, patient is advanced in time through the 'Wait Next Event PASI' module to the sooner of either Death or BSC or model end
- Costs and QALYs are assigned as in Trial Period arm



Step 4: BSC, death, or model end

- Patients enter BSC arm either at beginning of the model run or through discontinuation of treatment
- Similar to Trial Period and Apremilast Arm, with patients disposed of at the end
- The Excel read/write modules are also shown



Model Assumptions

- Patients who enter the BSC arm do not go back to apremilast therapy
- There are no changes to BSC or treatment paradigms of PsA in clinical practice over the time horizon of the model (5 years)
- The population to which the model is applied to follows the age and life expectancy of that in the model
- HAQ scores return to baseline after discontinuation of treatment
- No monitoring or lab costs for apremilast

Model limitations

- Data was sourced from clinical trials and not real world
- PASI is used as the trial period endpoint, but is not the clinical trial endpoint for efficacy
- Indirect costs of treatment are not accounted for in the model

Model results

		Control		Apremilast	
Rep		Costs	QALYs	Costs	QALYs
1.00		$ 30,558.54	19.70	$ 288,081.27	34.00
2.00		$ 107,698.74	53.81	$ 162,649.05	54.36
3.00		$ 66,412.11	36.19	$ 302,328.11	48.89
4.00		$ 139,131.43	68.18	$ 651,137.37	74.52
5.00		$ 32,584.15	17.74	$ 128,977.00	20.67
6.00		$ 86,104.37	45.88	$ 188,795.84	47.13
7.00		$ 75,148.61	38.87	$ 242,798.90	40.83
8.00		$ 94,376.35	50.68	$ 198,235.75	53.69
9.00		$ 99,138.22	53.90	$ 224,178.43	60.20
10.00		$ 96,838.01	57.71	$ 226,460.36	59.30
11.00		$ 75,393.11	41.54	$ 210,705.91	48.16
12.00		$ 106,148.80	55.74	$ 504,847.20	60.29
13.00		$ 103,474.64	50.81	$ 123,192.79	51.13
14.00		$ 73,509.76	37.78	$ 142,757.01	38.63
15.00		$ 113,050.81	64.10	$ 246,031.07	65.72
	Total	$ 1,299,567.67	692.65	$ 3,841,176.07	757.51
	Avg/Patient	$ 17,327.57	9.24	$ 51,215.68	10.10
			AVG	$ 33,888.11	0.86

Comparison of DES to Markov Model

- Model cost results are within 20%

	QALY/ patient	Cost/ patient
Markov Model	0.29	$41,338
DES	0.86	$33,888

Conclusions

- DES models are more adaptable, compared to Markov models
  - Once data becomes available, for example QOL instrument data, the DES is easily updated
- DES and Markov models share limitations, specifically the availability and quality of data
  - Markov models have less data requirements
- A comparison of two models with the same data shows differences that can be attributed to
  - time to event that was used to calculate drop off to BSC
  - distributions used for age and life expectancy

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1. Schafer. *Biochem Pharmacol*. 2012;83:1583
2. Serezani et al. *Am J Respir Cell Mol Biol*. 2008;39:127
3. Gottlieb et al. *J Am Acad Dermatol*. 2008;58:851
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13. Enbrel Prescribing Information, http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf
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